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CLINICAL REPORT

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Van Maldergem syndrome and Hennekam syndrome: Further delineation of allelic phenotypes

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Biallelic variants in *FAT4* are associated with the two disorders, Van Maldergem syndrome (VMS) ($n = 11$) and Hennekam syndrome (HS) ($n = 40$). Both conditions are characterized by a typical facial gestalt and mild to moderate intellectual disability, but differ in the occurrence of neonatal hypotonia and feeding problems, hearing loss, tracheal anomalies, and osteopenia in VMS, and lymphedema in HS. VMS can be caused by autosomal recessive variants in *DCHS1* as well, and HS can also be caused by autosomal recessive variants in *CCBE1* and *ADAMTS3*. Here we report two siblings with VMS and one girl with HS, all with *FAT4* variants, and provide an overview of the clinical findings in all patients reported with *FAT4* variants. Our comparison of the complete phenotypes of patients with VMS and HS indicates a resemblance of several signs, but differences in several other main signs and symptoms, each of marked importance for affected individuals.

KEYWORDS
ADAMTS3, CCBE1, DCHS1, FAT4, Hennekam syndrome, lymphedema, Van Maldergem syndrome

1 | INTRODUCTION

In 1989, Hennekam and co-workers reported a consanguineous family in which four members presented with facial anomalies, intellectual disability, lymphedema of the face, limbs and genitalia, and intestinal lymphangiectasia (Hennekam et al., 1989). Since then a total of 40 affected individuals have been reported with the same entity (Alders et al., 2013; Crawford et al., 2016). *CCBE1* has been found to be a causative gene (Alders et al., 2009; Connell et al., 2010), but variants in *CCBE1* can be detected in only 25% of patients (Alders et al., 2013). In two patients causative variants have been identified in *ADAMTS3* (Brouillard et al., 2017).

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In 1992, Van Maldergem and co-workers reported a girl with an unusual combination of clinical features: flat face, telecanthus, small ears, camptodactyly of fingers, interdigital webbing, joint hyperlaxity, neonatal hypotonia, and moderate intellectual disability (van Maldergem, Wetzburger, Verloes, Fourneau, & Gillerot, 1992). In total nine patients have been reported with a similar clinical presentation (Mansour et al., 2012; Neuhann et al., 2012; Zampino et al., 1994). Brain anomalies, especially a small callosal body and neuronal migration disturbances, and breathing anomalies were found to occur frequently. Through homozygosity mapping Cappello et al. mapped Van Maldergem syndrome (VMS) to 11p15.4 and 4q28.1 and found variants in *DCHS1* and *FAT4*, respectively (Cappello et al., 2013). Shortly thereafter homozygous variants in *FAT4* were also reported in a group of patients with Hennekam syndrome (HS) (Alders et al., 2014).

Here we report two siblings with VMS and an isolated patient with HS, and compare our findings with previously reported patients.

2 | METHODS

Patient 1 has been mentioned in short elsewhere (Alders et al., 2014; Bianchin, Tribi, Reverzani, Formigoni, & Polizzi, 2015). The patients and parents participating in the study have provided informed consent. Genomic DNA (gDNA) was isolated from blood leukocytes using the Maxwell 16 LEV DNA Blood purification kit (PromegaCorporation, Madison, WI) according to the manufacturer's instructions. Analysis of *FAT4* in Patients 1 and 2 was done by Sanger sequencing. All coding exons and flanking intronic regions of *FAT4* (NCBI Reference Sequences NG_016310.1 [genomic] and NM_001291303.1 [mRNA]) were PCR amplified (primer sequences available upon request) and amplicons were bi-directionally sequenced using the BigDye1Terminator Cycle Sequencing kit and ABI 3730XL DNA Analyzer (Applied Biosystems, Foster City, CA).

Analysis of *CCBE1* and *FAT4* in Patient 3 was done using a NGS panel for lymphedema (v2, 36 genes, Amsterdam Genome Dx). Target enrichment was done with custom designed in solution captures (SeqCap EZ Choice, Nimblegen) using Nimblegen Rebal algorithm and sequencing was done on an Illumina MiSeq. Paired-end sequencing reads (2×150 bp) were mapped to GRCh37/hg19 reference genome using BWA-MEM (0.7.5). Variants were identified using the HaplotypeCaller from GATK version 2.8.1 (Genome Analysis Toolkit, Broad Institute) along with Picard tools version 1.89.

Variant annotation is according to recommendations of the HGVS (http://varnomen.hgvs.org/). Nucleotide numbering reflects cDNA numbering with þ1 corresponding to the A of the ATG translation initiation codon in the reference sequence, with the initiation codon as codon 1. At protein level, þ1 corresponds to the first methionine residue (NP_001278232.1).

3 | PATIENTS

3.1 | Patient 1

The boy is the first-born child of healthy consanguineous (first cousins) parents of Moroccan origin. He was born at 41 weeks of gestation, after a pregnancy complicated by polyhydramnios and ascites. At birth, his weight was 2,760 g (<3rd percentile), length was 49 cm (10th to 25th percentile), and head circumference 35 cm (50th percentile). He had a marked airway obstruction and serious breathing difficulties from birth on, which required tracheostomy, and mandibular distractors were used because of his small jaw. He was found to have a conductive hearing loss. Echocardiography showed a patent foramen ovale that closed spontaneously.

As an infant, he had a long face, hypertelorism, proptosis, downslanting palpebral fissures, small ears, broad nasal ridge and tip, overlapping fingers, camptodactyly of the third finger on the left hand, and bilateral cutaneous syndactyly between the second and third toes (Figures 1a,b and 2a,f).

He demonstrated a slow psychomotor development, especially in language skills. He was sitting unaided at 8 months, and walked unaided at 18 months. At 23 months he was able to use a few simple words. At present day, the boy attends regular school with a special education assistance. His behavior is considered to be normal.

At the age of 2 years, re-evaluation showed his height and weight to have increased till the 25th percentile. Facially the proptosis had decreased, the downward slanting had increased, the nasal bridge had become more depressed, and the lower lip had become everted, while camptodactyly remained unchanged (Figures 1c,d and 2b). He had developed a mild ptosis. The forefeet had become adducted.

An MRI of his head demonstrated atresia of external auditory canals, periventricular heterotopias, thin corpus callosum, small olfactory bulbs, partial malrotation of hippocampus, and general reduction of white matter (Figure 3a,f,g). A temporal bone CT confirmed the bilateral external auditory canal atresia, underdeveloped tympanic cavities and absent pneumatization of the mastoids. Abdominal and pelvic ultrasound yielded normal results.

A full skeletal survey showed wormian bones of the skull, a narrow upper part of the thorax, short clavicles, thin ribs, delayed ossification of patellae, a delayed bone age, thin and pointed distal phalanges, and pedes adducti (Figure 3d,h–j). In addition, the boy presented a delayed primary teeth eruption, his first tooth having erupted at 26 months.

At 5 years and 4 months his height was 106 cm (25th percentile), weight 18 kg (25th percentile), and head circumference 50.5 cm (25th to 50th percentile). The clinical diagnosis of VMS was suspected. He received a middle ear implant for his hearing loss (Bianchin et al., 2015).

At 7 years 10 months of age his height was 122 cm (25th percentile), weight 30 kg (90th percentile), and head circumference 52 cm (25th to 50th percentile). At age 9 years his face showed a more marked hypertelorism, the ptosis had become more marked, also showing in elevated eyebrows, the broadness of nasal ridge and tip had decreased, and his face had become more flat (Figure 1e,f). He has shown a remarkable increase in weight, which was however not due to lymphedema. He had 10 primary and 2 secondary teeth, all of them malpositioned. Hands and feet were essentially unchanged (Figure 1d). Next to polyhydramnios and fetal ascites, no signs of lymphatic abnormalities and edema have been reported.

FIGURE 1 Facial characteristics of patients reported here: Patient 1 and 2—Van Maldergem syndrome; Patient 3—Hennekam syndrome. (a, b) Patient 1 at birth; (c, d) Patient 1 at age 2 years; (e, f) Patient 1 at 9 years; (g, h) Patient 2 at birth; (i, j) Patient 2 at age 1 year 8 months; (k, l) Patient 2 at age 5 years 5 month; (m–o) Patient 3 at age 7 years. [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Patient 2

She is the sister of Patient 1, and was born at 38 weeks, weighing 2,250 g (<3rd percentile), length 46 cm (10th percentile), and head circumference 30 cm (<3rd percentile). She had feeding difficulties, but no significant respiratory problems in the neonatal period. She presented with hypertelorism, epicanthi, slight proptosis, a short columella, full lips, highly arched palate, thick gums, and small, low-set ears, and atretic external auditory canals. She had overlapping fingers and bilateral second to third toe syndactyly (Figures 1g,h and 2i). X-rays demonstrated a narrow upper part of the thorax and thin ribs, similar to the findings in her brother (Figure 3e). Brain MRI showed underdevelopment of the anterior part of the corpus callosum and malrotation of the hippocampus, but no periventricular heterotopias. (Figure 3b,c)

Her motor development was only somewhat slow, just like her brother's (walking unaided at 17 months), but cognition was estimated to be a bit more impaired than in her brother. She also attends regular school with special education assistance. The girl is shy, and less communicative than her brother.

At 1 year and 8 months her height was 80 cm (25th percentile), weight 7,870 g (<3rd percentile), and head circumference 46 cm (10th percentile). The palpebral fissures had become more downward slanted,

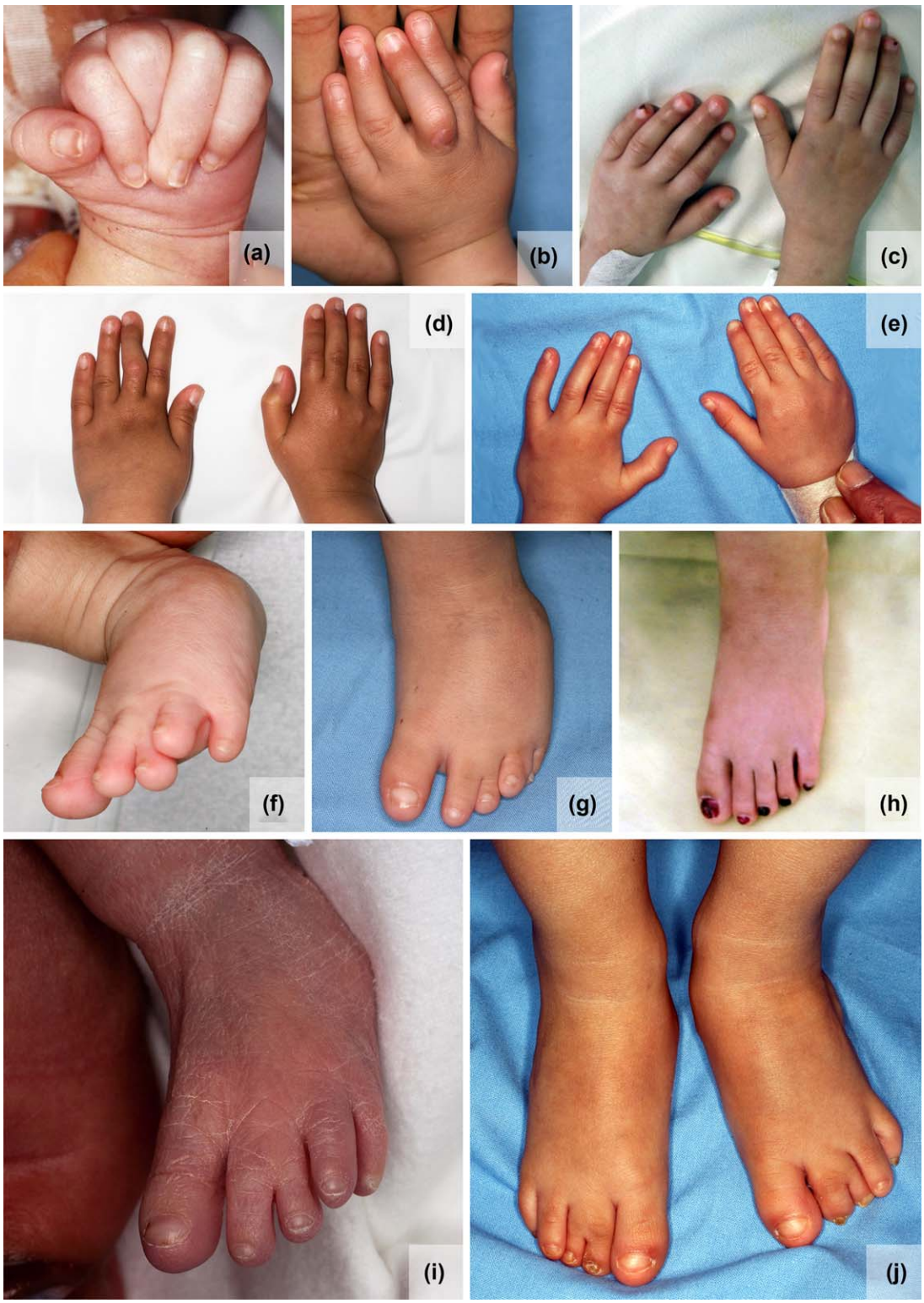

FIGURE 2 Limb characteristics of patients reported here: Patient 1 and 2—Van Maldergem syndrome; Patient 3—Hennekam syndrome. (a) Patient 1 at birth; (b) Patient 1 at age 2 years; (c) Patient 3 at age 7 years; (d) Patient 1 at age 8 years; (e) Patient 2 at age 1 year 8 months; (f) Patient 1 at birth; (g) Patient 1 at age 8 years; (h) Patient 3 at age 7 years; (i) Patient 2 at birth; (j) Patient 2 at age 1 year 8 months. [Color figure can be viewed at wileyonlinelibrary.com]

the nasal bridge more depressed, lips more pouting, and the face in general had become more flat, while mild camptodactyly of the fourth finger on the left had become more clear (Figures 1i,j and 2e,j). Her echocardiography and abdominal ultrasound were normal.

At age 4 years she had only three milk teeth (1 lateral incisor and 2 first molars, all of them lower), and no secondary ones. At age 5.5 years (Figure 1k,l), her face had become longer, she had developed a ptosis with elevated eyebrows, the

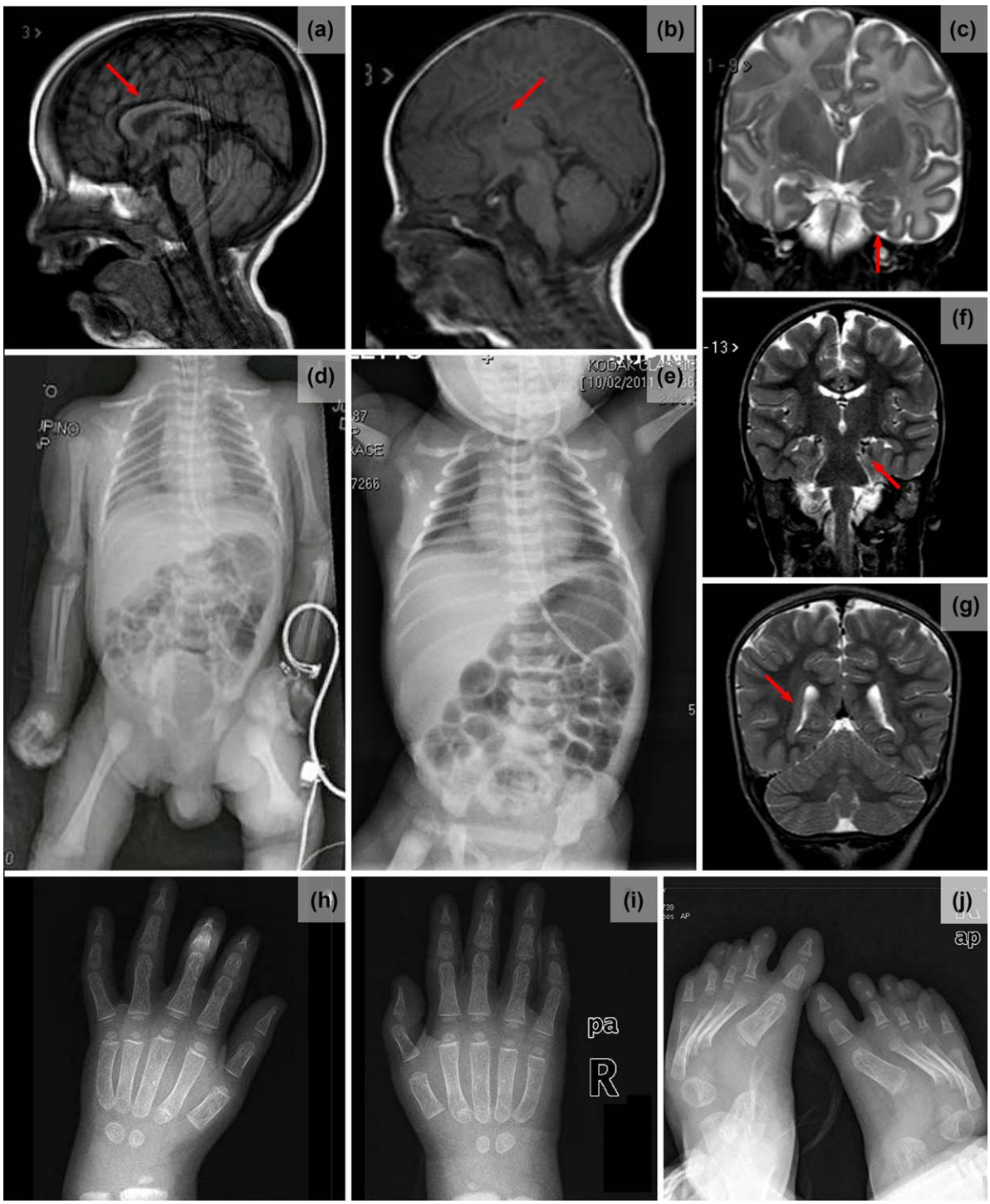

FIGURE 3 Radiological findings in patients reported here: Patient 1 and 2—Van Maldergem syndrome; Patient 3—Hennekam syndrome. (a) Patient 1 at age 5 years 5 months (underdeveloped callosal body); (b) Patient 2 at age 1 month (malformed callosal body); (c) Patient 2 at age 1 month (hippocampal malrotation); (d) Patient 1 at birth (narrow thorax, thin ribs); (e) Patient 2 at birth (narrow thorax, thin ribs); (f) Patient 1 at age 5 years 5 months (hippocampal malrotation); (g) Patient 1 at age 5 years 5 months (periventricular nodular heterotopia); (h) Patient 1 at age 2 years 4 months; (i) Patient 1 at age 2 years 4 months; (j) Patient 1 at age 2 years 4 months. [Color figure can be viewed at wileyonlinelibrary.com]

hypertelorism was more marked and the nasal tip less broad. She had five milk teeth and no secondary teeth. The distal limbs had remained essentially unchanged. There was no sign of peripheral lymphedema.

3.3 | Patient 3

The patient is the third of three children born to consanguineous parents (first cousins) of Iranian origin. Both parents and older siblings

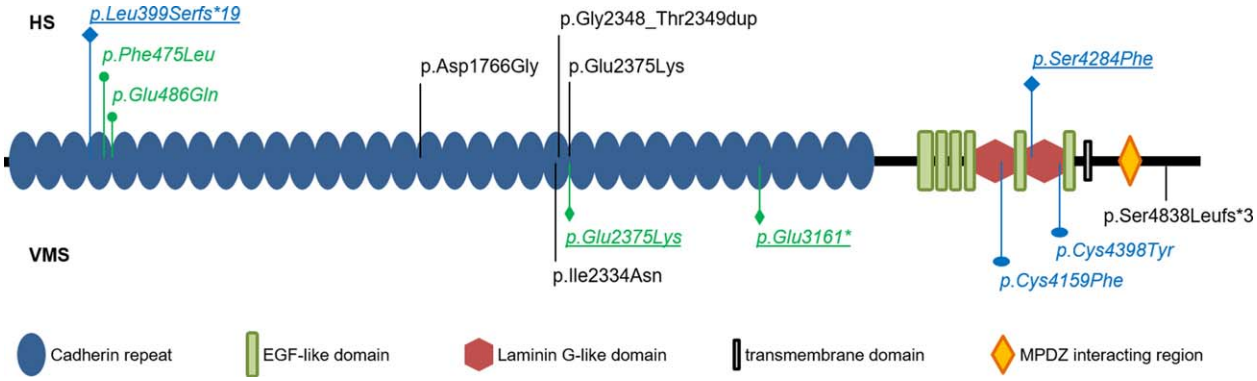

FIGURE 4 Schematic cartoon of the FAT4 protein, indicating mutations causing Hennekam syndrome (HS) above and Van Maldergem syndrome (VMS) below the cartoon. Homozygous mutations are indicated in black, and the four composite heterozygotes are in italics and matched by color-code: for each syndrome, mutations found in the same patient are indicated either in green or in blue. [Adapted from Alders et al., 2014]. [Color figure can be viewed at wileyonlinelibrary.com]

are healthy. She was born at term, weighing 2,600 g (3rd percentile), length was 46 cm (5th percentile), and head circumference was 32 cm (3rd percentile). At birth she presented respiratory distress and cyanosis which resolved spontaneously. No lymphedema was noticed at that time. In infancy she had recurrent respiratory and intestinal infections. She had her first teeth at the age of 14 months.

At 8 months she started developing generalized edema, for which she received albumin infusions. Additional studies showed low serum albumin—2.2 g/dL (3.4–5.2 g/dL), low serum protein—3.8 g/dL (6.6–8.9 g/dL), hypogammaglobulinemia: IgM < 0.25 g/L (0.56–2.18 g/L), IgG < 1.98 g/L (5.53–13.07 g/L); Hyper IgE—410.7 IU/L (0–200 IU/L), and eosinophilia (13.8%). Gastroduodenoscopy and colonoscopy were performed at age of 2 years. The duodenum revealed numerous tiny snow-white spots scattered in the second part and the third part. At colonoscopy mucosa was edematous and lacunar in appearance and scattered mild nodular mucosa with a whitish pit in the center was seen. Sigmoidoscopy showed fine nodularity. Histologic examination of the intestinal biopsies did not demonstrate dilated lymphatics. Transverse colon mucosa biopsy demonstrated lymphoid nodular hyperplasia.

Her motor development history was normal and similar to her unaffected older sisters. She could control her neck at 3 months, sit at 7 months and walk at 1 year. She started saying simple words at age 8 months, and used simple word sentences at age 2.5 years, but further language development such as making complex sentences was delayed till the age of 6 years. She showed improvement after speech therapy and school attendance at age 7, although her speech had not yet become similar to children of her age. Her cognition was formally assessed: her IQ was determined to be between 100 and 105. Her brain MRI did not show abnormalities.

At age 5 years, her height was 94 cm (<3rd percentile), weight was 13 kg (<3rd percentile), and her head circumference was 49 cm (10th to 25th percentile). She showed generalized pitting edema including some periorbital edema, abdominal distention, that became better by food restrictions in her diet according to clinical diagnosis of food allergy, a flat face, hypertelorism, thick eyebrows, synophrys, wide and flat nasal bridge, epicanthi, underdeveloped mid-face, small mouth with a somewhat full lower lip, conical teeth, gingival hypertrophy, mild retrognathia, low-set and small ears, and a low posterior hair line (Figures 1m–o and 2c,h). There was a distended abdomen, umbilical hernia, unilateral four-finger line, and persisting fetal pads, otherwise the limbs were normally formed. Ophthalmoscopy showed bilaterally blurred and elevated optic disks.

At age 7 years her height was 106 cm (<3rd percentile), weight was 17 kg (<3rd percentile), and her head circumference was 50 cm.

4 | MOLECULAR STUDIES

Classical cytogenetic analysis yielded normal karyotypes in the three patients. Array-CGH in Patients 1 and 2 did not show a chromosomal imbalance. Because of the small patellae in Patient 1 molecular analysis of *OCR1* (Meyer-Gorlin syndrome) was performed, yielding normal results. The clinical diagnosis of VMS in Patients 1 and 2 urged for molecular analysis of *FAT4* showing homozygosity for the variant c.7001T > A; p.Ile2334Asn in Patients 1 and 2. This variant has been reported previously (Alders et al., 2014) (Figure 4). It is absent in control populations (ExAC, 1000 genomes), and modifies an aminoacid residue in an evolutionary conserved position. In silico predictions suggest pathogenicity (SIFT score 0.002, PolyPhen2 scores 0.984 HumDiv/0.847 HumVar). Both parents were heterozygous.

Analysis of the 36 genes in the lymphedema gene panel in Patient 3 (diagnosis HS) demonstrated homozygosity for the variant c.5297A > G; p.Asp1766Gly in *FAT4*. This variant modifies an aminoacid residue in an evolutionary well conserved position and is absent in control populations (ExAC, 1000 genomes). In silico prediction programs suggest pathogenicity (SIFT score 0.015, PolyPhen2 scores 0.991 HumDiv/0.932 HumVar). Parents were not available for molecular analysis.

5 | DISCUSSION

We present here two patients with VMS and one with HS with *FAT4* mutations, and compare these to the earlier reported patients with

TABLE 1 Comparison of presently reported patients and patients reported in literature with Van Maldergem syndrome and Hennekam syndrome, subdivided by causative gene

	Van Maldergem syndrome*							Hennekam syndrome												
		FAT4																	ADAMTS3	
		This study		Neuhann et al. (2012)	Mansour et al. (2012)				Alders et al. (2014)									This study	CCBE1	Brouillard et al. (2017)
Family Individual	DCHS1	P1	P2	P1	P1	P6	Total	Total	F1-1	F1–2	F1–3	F1–4	F2-1	F2-2	F3-1	F4-1	F5-1	P3		
Psychomotor developmental delay	4/4	+	+	+	+	+	5/5	8/10	+	+	+	+	−	−	+	+	+	+	9/13	na
Short stature	2/2	−	−	+	+	+	3/5	6/10	+	−	+	+	+	+	−	−	−	+	9/13	1/2
Microcephaly	1/2	−	−	+	na	+	2/4	1/9	−	na	+	−	−	−	−	−	−	−	6/13	na
PVNH[a]	2/4	+	−	−	+	−	2/5	0/1										−	na	na
Neonatal hypotonia	3/3	+	+	+	+	+	5/5	1/10	−	−	−	−	−	−	na	+	−	−	1/13	na
Unusual face	4/4	+	+	+	+	+	5/5	10/10	+	+	+	+	+	+	+	+	+	+	13/13	2/2
Hypertelorism	4/4	+	+	+	+	+	4/4	10/10	+	+	+	+	+	+	+	+	+	+	13/13	2/2
Epicanthus	4/4	+	+	+	−	+	4/5	10/10	+	+	+	+	+	+	+	+	+	+	11/13	2/2
Blepharophimosis	4/4	−	−	+	+	+	3/5	7/10	+	+	+	+	−	−	+	+	−	+	6/13	0/2
Flat nasal bridge	4/4	+	+	+	+	+	5/5	9/10	+	+	+	+	+	+	−	+	+	+	11/13	2/2
Small mouth	4/4	+	+	+	−	+	4/5	7/10	+	−	−	−	+	+	+	+	+	+	7/13	0/2
Irregular dentition	3/3	+	+	+	+	na	4/4	9/9	+	+	+	+	+	+	na	+	+	+	12/13	na
Small ears	4/4	+	+	+	+	+	5/5	9/9	+	+	+	+	+	+	na	+	+	+	13/13	0/2
Hearing loss	4/4	+	+	+	+	+	5/5	2/10	−	−	−	−	+	+	−	−	−	−	0/13	na
Tracheal anomalies	4/4	+	−	+	+	+	4/5	0/10	−	−	−	−	−	−	−	−	−	−	0/13	0/2
Feeding difficulties	4/4	+	+	+	+	+	5/5	na											na	1/2
Camptodactyly	4/4	+	+	+	+	+	5/5	5/9	+	−	+	+	+	+	na	−	−	−	5/13	na
Syndactyly	0/4	+	+	+	−	−	3/5	2/9	−	−	−	−	+	−	na	+	−	−	4/13	na
Lymphedema limbs	0/4	−	−	−	+	−	1/5	10/10	+	+	+	+	+	+	+	+	+	+	13/13	2/2
Lymphangiectasia gut	0/4	−	−	−	−	−	0/5	8/10	+	+	+	+	+	−	−	+	+	+	13/13	1/2
Lymphangiectasia other	0/4	−	−	−	−	−	0/5	8/10	+	+	+	+	+	−	+	+	−	+	0/13	2/2
Cardiac malformation	2/4	−	−	+	−	−	1/5	0/10	−	−	−	−	−	−	−	−	−	−	2/13	0/1
Small kidneys	3/4	−	−	+	+	+	3/5	0/8	−	−	na	−	−	−	na	−	−	−	0/4	na
Osteopenia	2/4	+	+	+	+	+	5/5	2/10	−	+	−	−	−	−	−	+	−	−	0/8	na

Note. Data from individuals with *DCHS1* mutations are from references Mansour et al. (2012), and data from *CCBE1* mutations are from references Alders et al. (2014).
*Included only patients with molecularly confirmed diagnosis and with detailed clinical description; [a]PVNH = periventricular nodular heterotopia; + present; − absent; na = not available.

either VMS or HS. To date, 9 patients with VMS (7 molecularly confirmed) and 40 patients with HS (23 molecularly confirmed) have been reported (Table 1). Two additional VMS patients have been published without detailed clinical information (Cappello et al., 2013). Other VMS patients reported to date harbored variants in *DCHS1*, while 13 cases of HS are caused by variants in *CCBE1*, and 2 patients with variants in *ADAMTS* (Janssen et al., 2016). For the remaining patients with HS, causative mutations have not been detected.

The unusual face, which consists of hypertelorism, epicanthus, flat nasal bridge, irregular dentition, and small ears, is the common feature for both conditions. The phenotype is variable in both entities however, also within a single family, although the phenotype in VMS patients shows less variation compared to the phenotype in HS patients. The resemblance between patients with VMS and HS harboring mutations in *FAT4* was noted previously (Alders et al., 2014).

Other main differences between the two entities are the feeding and breathing difficulties, which were common in patients with VMS and absent in patients with HS. All patients with VMS had feeding difficulties at birth, and all but one presented breathing difficulties caused by tracheal anomalies, with the majority of patients requiring tracheostomy. Intellectual disability occurs in both entities, typically moderate to severe in VMS and mild in HS, but variability has been more marked in HS, also within a single family.

Periventricular heterotopia is an important diagnostic criterion for VMS (Cappello et al., 2013). These authors suggested that migration anomalies in VMS patients are caused directly by mutations in *DCHS1* and *FAT4*. We found periventricular heterotopia in half of all patients with VMS, both those with a *FAT4* and those with a *DCHS1* mutation. Other MRI findings in VMS have been an underdeveloped corpus callosum, hippocampal malrotation, and small olfactory bulbs (Figure 3). In HS most reported patients had no neurological abnormalities that would require MRI examination, and therefore brain MRI data are not available (Alders et al., 2014). It cannot be excluded that similar, but asymptomatic brain findings are present in patients with HS as well.

Camptodactyly has been present in all VMS patients reported to date, including ours (Figure 2a,b,d,e). Unlike the majority of reported patients, none of the siblings presented interphalangeal webbing. Furthermore, the patient with HS did not present digit anomalies. Cutaneous syndactyly has been reported in similar frequencies in VMS and HS, and camptodactyly has been mentioned more frequent in VMS. Due to small numbers these associations remain uncertain however.

General osteopenia is common in VMS: all five patients with mutations in *FAT4* presented osteopenia, and two of four patients with mutations in *DCHS1* presented it. In 2 of 18 patients with HS (both with *FAT4* mutation) osteopenia was noticed. Small kidneys are common in patients with VMS, while no patients with HS are known to us to have kidney anomalies. *DCHS1* and *FAT4* play an important role in kidney development (Bagherie-Lachidan et al., 2015; Mao, Francis-West, & Irvine, 2015), but at present the reason for absence of kidney abnormalities in HS remains uncertain.

Lymphedema and lymphangiectasia are hallmarks of HS. *CCBE1* and *ADAMTS3* are known to be involved in lymphangiogenesis and venous sprouting (Hogan et al., 2009; Janssen et al., 2016). Lymphedema caused by *CCBE1* is already present at birth, while patients harboring mutations in *FAT4* can have lymphedema onset later in childhood. On the contrary, one patient with VMS presented minimal lymphedema of the hand (Mansour et al., 2012), and in another patient in this publication (Patient 5) there seems to be infra-orbital edema, although this was not mentioned in the manuscript itself. Presence of lymphatic anomalies remains the biggest, and most important difference between these two conditions. As almost all patients with VMS were still young when reported it remains possible that lymphedema will develop in VMS individuals at a later age. No genotype-phenotype correlation has been defined to date.

During the follow-up of the present VMS patients we noted that their phenotype and other features changed over time. Some features, such as breathing and feeding difficulties, hypotonia, and camptodactyly were present at birth and infancy, but not in later life, while the typical facial gestalt became much more recognizable during the second to fourth years of life.

When comparing the total phenotypes of patients with VMS and HS we conclude that there are many resemblances, but the differences in signs and symptoms remain of marked importance to affected individuals. Lymphedema remains the main clinical sign which separates the two entities. Other, less prominent, but still important features are tracheal anomalies, intellectual disability, hearing loss, osteopenia, and kidney anomalies which have been much more frequent in VMS. In our opinion it seems prudent that because of the marked differences in consequences of the two diagnoses for affected individuals and their families to keep the two entities separate at present.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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REFERENCES

Alders, M., Al-Gazali, L., Cordeiro, I., Dallapiccola, B., Garavelli, L., Tuysuz, B., ... Hennekam, R. C. (2014). Hennekam syndrome can be caused by FAT4 mutations and be allelic to Van Maldergem syndrome. *Human Genetics*, *133*(9), 1161–1167. https://doi.org/10.1007/s00439-014-1456-y

Alders, M., Hogan, B. M., Gjini, E., Salehi, F., Al-Gazali, L., Hennekam, E. A., ... Hennekam, R. C. (2009). Mutations in CCBE1 cause generalized lymph vessel dysplasia in humans. *Nature Genetics*, *41*(12), 1272–1274. https://doi.org/10.1038/ng.484

Alders, M., Mendola, A., Ades, L., Al-Gazali, L., Bellini, C., Dallapiccola, B., ... Hennekam, R. C. (2013). Evaluation of clinical manifestations in

patients with severe lymphedema with and without CCBE1 mutations. *Molecular Syndromology*, *4*(3), 107–113. https://doi.org/10.1159/000342486

Bagherie-Lachidan, M., Reginensi, A., Pan, Q., Zaveri, H. P., Scott, D. A., Blencowe, B. J., … McNeill, H. (2015). Stromal Fat4 acts non-autonomously with Dchs1/2 to restrict the nephron progenitor pool. *Development*, *142*(15), 2564–2573. https://doi.org/10.1242/dev.122648

Bianchin, G., Tribi, L., Reverzani, A., Formigoni, P., & Polizzi, V. (2015). Original solution for middle ear implant and anesthetic/surgical management in a child with severe craniofacial dysmorphism. *Case Reports in Otolaryngology*, *2015*, 205972. https://doi.org/10.1155/2015/205972

Brouillard, P., Dupont, L., Helaers, R., Coulie, R., Tiller, G. E., Peeden, J., … Vikkula, M. (2017). Loss of ADAMTS3 activity causes Hennekam lymphangiectasia-lymphedema syndrome 3. *Human Molecular Genetics*, *26*(21), 4095–4104. https://doi.org/10.1093/hmg/ddx297

Cappello, S., Gray, M. J., Badouel, C., Lange, S., Einsiedler, M., Srour, M., … Robertson, S. P. (2013). Mutations in genes encoding the cadherin receptor-ligand pair DCHS1 and FAT4 disrupt cerebral cortical development. *Nature Genetics*, *45*(11), 1300–1308. https://doi.org/10.1038/ng.2765

Connell, F., Kalidas, K., Ostergaard, P., Brice, G., Homfray, T., Roberts, L., … Jeffery, S. (2010). Linkage and sequence analysis indicate that CCBE1 is mutated in recessively inherited generalised lymphatic dysplasia. *Human Genetics*, *127*(2), 231–241. https://doi.org/10.1007/s00439-009-0766-y

Crawford, J., Bower, N. I., Hogan, B. M., Taft, R. J., Gabbett, M. T., McGaughran, J., & Simons, C. (2016). Expanding the genotypic spectrum of CCBE1 mutations in Hennekam syndrome. *American Journal of Medical Genetics Part A*, *170*(10), 2694–2697. https://doi.org/10.1002/ajmg.a.37803

Hennekam, R. C., Geerdink, R. A., Hamel, B. C., Hennekam, F. A., Kraus, P., Rammeloo, J. A., & Tillemans, A. A. (1989). Autosomal recessive intestinal lymphangiectasia and lymphedema, with facial anomalies and mental retardation. *American Journal of Medical Genetics*, *34*(4), 593–600. https://doi.org/10.1002/ajmg.1320340429

Hogan, B. M., Bos, F. L., Bussmann, J., Witte, M., Chi, N. C., Duckers, H. J., & Schulte-Merker, S. (2009). Ccbe1 is required for embryonic lymphangiogenesis and venous sprouting. *Nature Genetics*, *41*(4), 396–398. https://doi.org/10.1038/ng.321

Janssen, L., Dupont, L., Bekhouche, M., Noel, A., Leduc, C., Voz, M., … Colige, A. (2016). ADAMTS3 activity is mandatory for embryonic lymphangiogenesis and regulates placental angiogenesis. *Angiogenesis*, *19*(1), 53–65. https://doi.org/10.1007/s10456-015-9488-z

Mansour, S., Swinkels, M., Terhal, P. A., Wilson, L. C., Rich, P., Van Maldergem, L., … Newbury-Ecob, R. (2012). Van Maldergem syndrome: Further characterisation and evidence for neuronal migration abnormalities and autosomal recessive inheritance. *European Journal of Human Genetics*, *20*(10), 1024–1031. https://doi.org/10.1038/ejhg.2012.57

Mao, Y., Francis-West, P., & Irvine, K. D. (2015). Fat4/Dchs1 signaling between stromal and cap mesenchyme cells influences nephrogenesis and ureteric bud branching. *Development*, *142*(15), 2574–2585. https://doi.org/10.1242/dev.122630

Neuhann, T. M., Muller, D., Hackmann, K., Holzinger, S., Schrock, E., & Di Donato, N. (2012). A further patient with van Maldergem syndrome. *European Journal of Medical Genetics*, *55*(6–7), 423–428. https://doi.org/10.1016/j.ejmg.2012.02.012

van Maldergem, L., Wetzburger, C., Verloes, A., Fourneau, C., & Gillerot, Y. (1992). Mental retardation with blepharo-naso-facial abnormalities and hand malformations: A new syndrome?. *Clinical Genetics*, *41*(1), 22–24.

Zampino, G., Colosimo, C., Balducci, F., Mariotti, P., Serra, F., Scarano, G., & Mastroiacovo, P. (1994). Cerebro-facio-articular syndrome of Van Maldergem: Confirmation of a new MR/MCA syndrome. *Clinical Genetics*, *45*(3), 140–144.

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